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CLINICAL REPORT

Clinical Manifestations of Cutaneous Graft-versus-host Disease after Allogeneic Haematopoietic Cell Transplantation: Long-term Follow-up Results in a Single Turkish Centre

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The aim of this study was to evaluate the clinical manifestations of cutaneous graft-versus-host disease (GVHD) developed after allogeneic haematopoietic cell transplantation. In all, 67 patients were evaluated: 49 patients developed acute GVHD, 17 patients developed *de novo* chronic GVHD and 29 developed secondary chronic (15 limited, 14 progressive) GVHD following acute cutaneous GVHD. Of the 46 patients with chronic GVHD, lichenoid lesions were observed in 32 and sclerodermoid lesions were observed in 12. In four patients with sclerodermoid cutaneous GVHD, these lesions occurred after a lichenoid phase. Oral lesions were present in 61% of the patients and six of them had only oral mucosal involvement without any skin lesions. Nail lesions were observed in 31% of the patients. During the follow-up period 15 patients with GVHD died and in 7 of them the cause of death was related to chronic GVHD. In conclusion, GVHD has a wide spectrum of cutaneous manifestations, which can be used as an important tool for the early diagnosis of the disease. ***Key words: graft-versus-host disease; skin.***

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Graft-versus-host disease (GVHD) is one of the most important complications of allogeneic haematopoietic cell transplantation and despite tremendous efforts in prevention and treatment, it is still associated with significant morbidity and mortality. The skin, gastrointestinal tract and liver are the organs primarily affected.

The essential requirements for the development of GVHD: (i) the graft must contain immunocompetent cells; (ii) the immune system of the host must be incapable of reacting to foreign antigens; and (iii) the host and the donor cells should have antigenic differences (1).

Although GVHD may develop after autologous and syngeneic stem cell transplantations, these transplantations are relatively rare when compared with allogeneic haematopoietic cell transplantation (AHCT) (2, 3).

In recent years many studies have been designed to illuminate the pathogenesis of the disease. Acute and chronic GVHD occur as a result of an immunological reaction between the donor T lymphocytes and the tissues of an immuno-incompetent host (4).

The immune system itself is a major target for chronic GVHD and the development of dysfunction may lead to autoimmune disorders. Therefore, chronic GVHD may be a good model for understanding the pathogenesis of other autoimmune skin diseases such as vitiligo, alopecia areata and scleroderma.

Today, many risk factors responsible for the development of GVHD are well known but the disease is still an important problem for the transplant team, as it occurs at an incidence of 40–70% of patients depending on the degree of HLA mismatch. Although GVHD mostly arises after AHCT, it may also be observed after the use of non-irradiated blood products, after solid organ transplantations and as neonatal GVHD in infants with congenital immunodeficiency (5–9).

Skin is the most frequently affected organ in both acute and chronic GVHD and is significantly associated with morbidity and mortality.

The purpose of this study was to investigate the clinical findings of patients who underwent AHCT and developed acute and/or chronic GVHD.

PATIENTS AND METHODS

Between April 1992 and April 2002, 256 patients underwent AHCT at the Stem Cell Transplantation Unit of Ankara University. Our study group consisted of 67 patients (39 men, 28 women) who developed acute and/or chronic GVHD after transplantation. Their median age was 29 years (range 14–46). The main indications for transplantation were almost all standard risk patients with haematological malignancies. Characteristics of the patients and donors are given in Table I. Thirty-six of the healthy sibling donors were men, 31 were women, with a median age of 28 years (range 12–50).

The stem cell source was bone marrow in 32 (47.8%) and peripheral blood stem cells in 35 (52.2%) patients. A sex mismatch between donor and recipient was present in 35 (52.2%) patients and AB0 blood group mismatch in 26 (38.8%) patients. All except three patients received a conditioning regimen including busulphan (16 mg/kg) and cyclophosphamide (120 mg/kg). The other three patients

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Table I. *Characteristics of the donors and recipients with cutaneous graft-versus-host disease (n=67; 39 men, 28 women)*

Age (years)	
median	29
range	14–46
Age distribution (*n*)	
0–20 years	11
21–40 years	42
≥41years	14
Diagnosis (*n*)	
Acute myeloblastic leukaemia	27
Chronic myelogenous leukaemia	35
Acute lymphoblastic leukaemia	2
Myelodysplastic syndrome	2
Sphingolipidosis	1
Haematopoietic stem cell source (*n*)	
Bone marrow	32
Peripheral stem cell	35
Pretreatment regimen (*n*)	
Bu+cyclophosphamide	64
Flu+ATG+ARA-C or Bu	3
Donor–recipient sex mismatch (*n*)	35
Female donor/male recipient (*n*)	12
AB0 blood group mismatch (*n*)	26

Bu, busulphan; Flu, fludarabine; ATG, antithymocyte globulin; ARA-C, cytosine arabinoside.

received a reduced conditioning regimen (fludarabin+antithymocyte globulin+cytosine arabinoside or busulphan). Cyclosporine (3 mg/kg/day i.v.) and short-term methotrexate (day +1; 15 mg/m^2, days +3, +6±11; 10 mg/m^2) were given to all patients for GVHD prophylaxis.

Dermatological evaluations were performed by one specialist before transplantation (baseline) and then periodically and whenever indicated after transplantation. The diagnosis of cutaneous GVHD was established on both clinical and dermatopathological findings.

Evaluation of the risk factors for cutaneous GVHD

We evaluated some of the risk factors known to be related to the development of GVHD, such as recipient–donor sex mismatch, recipient age and ABO blood group mismatch. The results were analysed statistically by χ^2 test.

RESULTS

Twenty-nine of the 67 (43%) patients who underwent AHCT developed secondary chronic cutaneous GVHD following acute cutaneous GVHD. Twenty-one patients developed only acute cutaneous GVHD and in 17 patients *de novo* chronic cutaneous GVHD occurred without previous acute GVHD (see Fig. 1 for clinical examples).

Donors and recipients were sex-mismatched in 35 (52.2%) cases and ABO blood group mismatch was found in 26 (38.8%) cases. We did not find any statistically significant difference for developing chronic cutaneous GVHD between sex-matched and mismatched patients ($p=0.71$) or ABO blood group identical and non-identical patients ($p=0.07$). Haematopoietic stem cell source was bone marrow in 32 patients and peripheral blood stem cells in 35 patients, with no statistical difference regarding the number of patients in each group ($p=0.71$).

Clinical features of acute cutaneous GVHD

Forty-nine patients developed acute cutaneous GVHD within a mean period of 30.4±21.8 days (range 5–90) post-transplant (Table II). Clinical grading of acute GVHD in these patients showed grade 1 disease (erythematous maculopapular eruption over <25% of body area) in 31 (63.3%), grade 2 disease (erythematous maculopapular eruption over 25–50% of body area) in 14 (28.6%), grade 3 disease (erythroderma) in 3 (6.1%) and grade 4 disease (bullae or generalized epidermal necrolysis) in 1 (2%) patient. Four of the patients experienced pain and four suffered from itching as subjective complaints.

One patient with lichenoid papules developed progressive chronic GVHD. Another patient with generalized erythema multiforme-like lesions also developed progressive chronic GVHD. Direct immunofluorescent studies of bullous lesions were negative for immunoglobulins (IgG, IgM, IgA) and complement (C_3).

Clinical features of chronic cutaneous GVHD

Chronic cutaneous GVHD developed in 46 (68.7%) patients within a mean period of 9.5±9.9 months (range 40 days to 3.5 years) after transplantation (Table II). Chronic cutaneous GVHD evolved from acute GVHD in 14 (30.4%) patients, occurred after a disease-free interval in 15 (32.6 %) patients and occurred *de novo* in 17 (37%) patients.

Thirty-two (69.6%) patients with chronic cutaneous GVHD presented lichenoid GVHD. Four of these progressed into the sclerodermoid form. Sclerodermoid GVHD was observed in 12 (26%) patients. All the patients with lichenoid GVHD suffered itching as a subjective complaint.

Involvement of the oral mucosa was observed in 28 (60.9%) patients (Table III). Six patients had only oral lesions without any skin lesion, whereas 22 patients had both oral and skin lesions. The localizations of the lesions were tongue, buccal mucosa, lips and gingivae.

Nail involvement occurred in 21 (45.6%) patients (Table III). The most frequent findings were longitudinal streaks and roughness resembling nail changes in lichen planus (Table III).

Clinical classification of patients according to the degree of skin and organ involvement showed limited disease (skin and/or liver involvement) in 14 (30.4%), and extensive disease (multi-organ involvement) in 32 (69.6%) patients.

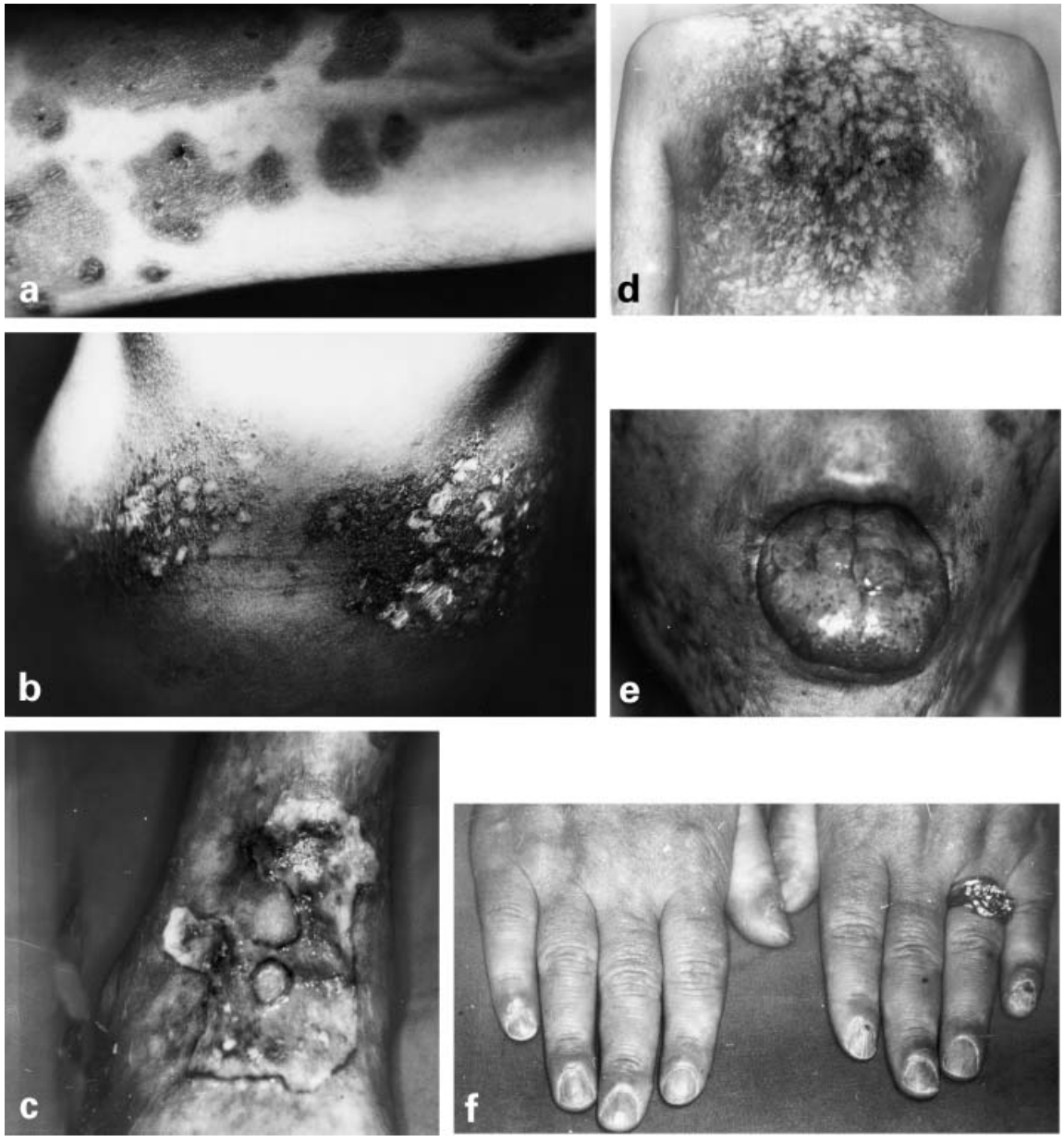

Fig. 1. Skin manifestations in graft-versus-host disease (GVHD). (a) Erythema multiforme-like lesions in acute GVHD. (b) Dermatomal lichenoid GVHD. (c) Ulceration on a sclerotic surface. (d) Poikilodermic lesions in sclerodermoid chronic GVHD. (e) Oral mucosa involvement in chronic GVHD (erosions on tongue and pyogenic granuloma formation). (f) Periungual erythema, pterygium, onychoatrophy, longitudinal streaks and lunula ulceration in a patient with chronic GVHD.

Cutaneous GVHD mortality

The mean follow-up period was 38.82 ± 28.14 months (range 5 – 122). During the follow-up period, 7 (46.7%) patients died because of chronic GVHD, 3 (20%) patients died because of the complications related to acute GVHD, 4 (26.7%) patients died because of relapses and 1 (6.7%) patient died because of the progression of the primary disease. The patients who died with chronic GVHD had extensive involvement.

Although the cutaneous involvement was not the primary cause of mortality in any of these patients it had a significant impact on morbidity and decreased the quality of life.

DISCUSSION

GVHD has two distinct clinical manifestations: acute GVHD and chronic GVHD. Acute GVHD occurs in 40 – 50% of patients after AHCT and in 5 – 30% of patients after syngeneic haematopoietic cell transplantation (10, 11). The incidence of the development of chronic GVHD after AHCT is 30 – 50% (4).

Various risk factors have been defined for the development of GVHD. Both major and minor HLA mismatch significantly increase the incidence. Even in optimal conditions (HLA full-matched, sibling donor) the incidence of the development of stage 2 – 4 acute GVHD is still 40 – 50% (12 – 14). All our patients had

Table II. *Skin manifestations observed in acute and chronic graft-versus-host disease*

Skin manifestation	*n* (%)
Acute (*n* = 49)	
Erythema, hyperpigmentation and desquamation limited to axillae and groin	27 (55.1)
Erythematous maculopapular eruption over the trunk	14 (28.5)
Acral erythema	7 (14.2)
Erythema and oedema of the face	3 (6.1)
Localized epidermal necrolysis involving the ear	1 (2)
Generalized erythema multiforme-like eruption	1 (2)
Lichenoid papules	1 (2)
Perifollicular papules	1 (2)
Chronic (*n* = 46)	
Purple-violaceous lichenoid papules and plaques	20* (43.4)
Sclerosis	12† (26)
Hyperpigmentation	14 (30.4)
Poikiloderma	4 (8.6)
Xerosis	12 (26)
Ulceration	2 (4.3)
Bullae	1 (2.1)
Acquired ichthyosis	1 (2.1)
Vitiligo	2 (4.3)
Keratosis pilaris	2 (4.3)
Alopecia	21 (45.6)

*Localized over the previous herpes zoster cicatrix area in two patients.
†Six generalized, six localized.

HLA identical sibling donors and were standard risk patients for their underlying diseases.

The risk of GVHD increases with respect to the increase in the host's age (15, 16). In our series, 81% of the patients were over 20 years in age and the incidence of chronic GVHD showed a peak in the 21–40-year-old age group (42 patients, 62.7%). The gender of both donor and recipient affects the development of GVHD.

Table III. *Oral and nail lesions observed in chronic GVHD*

Lesion	*n* (%)
Oral lesions (*n* = 28)	
White plaques	16 (57.1)
White reticular lesions	6 (21.4)
Erosions/ulcers	15 (53.5)
Hyperaemia	4 (14.2)
Xerostomia	6 (21.4)
Pyogenic granuloma	1 (3.5)
Gingivitis	1 (3.5)
Nail lesions (*n* = 21)	
Longitudinal streaks	16 (76.1)
Roughness	12 (57.1)
Fragility	6 (28.5)
Onycholysis	1 (4.7)
Pterygium	3 (14.2)
Lunula ulceration	1 (4.7)
Onychoatrophy	3 (14.1)
Periungual erythema	1 (4.7)
Opacity/thickening of the nail plate	1 (4.7)

The risk of GVHD increases when the transplantation is performed from a female donor to a male host (17). However, we did not observe a significant influence of donor sex, recipient–donor sex mismatch and ABO blood group mismatch in our patients who developed cutaneous GVHD.

GVHD prophylaxis is of the utmost importance; the risk of GVHD rises to 70–100% in patients who do not receive specific prophylaxis (18, 19). There are various prophylaxis regimens. A short-term methotrexate/cyclosporine prophylaxis regimen is used routinely in our stem cell transplantation unit. In our study group one patient who discontinued this therapy developed stage 3 acute GVHD (skin and gastrointestinal involvement) and died 4 months after transplantation.

Acute GVHD arises 7–45 days (mean period 21 days) after AHCT. A few cases develop acute GVHD characterized by severe generalized inflammation within the first week, which is known as hyper-acute GVHD (4). In acute GVHD, skin manifestations are usually the first and the most frequent findings. Arslan et al. (20) reported a 96.5% rate of skin involvement in acute GVHD. In our series of 49 (73.1%) acute GVHD cases, the mean time of onset was 30.44 ± 21.75 days.

In acute GVHD the most frequent skin manifestation is erythematous eruption with pruritus and/or burning sensation involving palms and soles, earlobe, neck and the upper back. Early lesions are characterized by folliculocentric erythematous pale maculae and papules, and may involve broad areas (4, 21). We observed erythematous maculopapular rash regressing with hyperpigmentation and desquamation involving axillae and groin, trunk, neck, face, earlobe, and palms and soles. Axillae and groin were the most frequently involved areas. Cutaneous GVHD may sometimes begin with a widespread morbilliform rash suggesting acute GVHD, then rapidly transform into lichenoid and sclerodermoid forms (4). In one of our patients cutaneous GVHD began with widespread erythema multiforme-like erythematous-bullous lesions (Fig. 1a) and, without improvement, turned into lichenoid and then sclerodermoid chronic GVHD. In another patient, lichenoid drug eruption-like lesions progressed into lichenoid chronic GVHD.

In severe acute GVHD, exfoliative dermatitis or toxic epidermal necrolysis-like lesions may also develop (4, 21, 22). Epidermal necrosis can be seen in approximately 6% of acute GVHD patients, either confined to small areas subjected to pressure or spread out (21–23). We observed only one case of localized epidermal necrolysis involving the earlobe.

In the literature, acute follicular GVHD is reported to be frequent and to begin in earlier phases (24, 25). In one of our patients, perifollicular papular lesions were the first and the only lesions of acute GVHD.

While acral erythema may be an adverse effect of

some chemotherapeutic agents such as 5-FU, folinic acid and IFN-α, it may also be a sign of acute GVHD (26). We observed acral erythema in three of our acute GVHD patients.

Chronic GVHD occurs within 40 days to 4 months (mean period 100 days) post-transplant, with a frequency of 30–50% following AHCT. In chronic GVHD the skin involvement rate is reported to be about 90–100% (4). It is also reported that the incidence of chronic cutaneous GVHD may alter in genetically different populations, and was found to be lower in Japanese patients (28%) than American and European patients (79–90%) (27). In Turkey, Arslan et al. (20) reported the incidence of chronic GVHD as 70% in 20 non-lymphoblastic leukaemia patients who underwent allogeneic peripheral stem cell transplantation.

In 46 patients with chronic cutaneous GVHD in clinical follow-up, the mean period for onset of the lesions was 9.5 ± 9.9 months (range 40 days to 3.5 years) after transplantation. In the literature the longest period for the development of chronic GVHD was reported to be 15 months (22).

Acute GVHD is a risk factor for chronic GVHD (1, 4). A study pointed out that 25% of chronic GVHD developed *de novo* without preceding acute GVHD, 60% evolved from grade I and 80% from grade I–IV acute GVHD (1). In another study, the incidence of progressive chronic GVHD was reported to be 32%, quiescent chronic GVHD, 36%, and *de novo* commencement 30% (21). Nevertheless some investigators stated that acute GVHD was not a risk factor for the development of chronic GVHD (27). In our study, chronic GVHD developed in 63% of the patients with acute cutaneous GVHD (30.4% progressive; 32.6% quiescent). *De novo* commencement was observed in 37% of our chronic cutaneous GVHD patients. These rates are close to those reported in the literature (1, 4, 21).

In chronic GVHD, skin is the most frequent target organ but oral and ocular mucosa, submucosal glands and liver involvement are also common (1, 4). Skin lesions in chronic GVHD occur either as lichenoid or sclerodermoid types (4, 21, 22). We observed lichenoid chronic GVHD in 32 patients (69.6%) with cutaneous chronic GVHD, which evolved into the sclerodermoid form in 4 patients. In all, 12 patients (26.1%) experienced sclerodermoid chronic GVHD.

Lichenoid chronic GVHD appears earlier and lesions are easily recognizable. Its purple/violet-coloured papules and plaques can hardly be differentiated from classical lichen planus (4, 21). In two of our patients lichenoid lesions were intensified on a scar area originating from a former herpes zoster infection (Fig. 1b). Lichenoid GVHD in a dermatomal distribution has also been reported in a few cases (28, 29).

Sclerodermoid chronic GVHD appears late in the course of the disease and begins with indurated and sclerotic, bright white plaques with indefinite margins. Patchy hyperpigmentation and poikilodermic alterations develop rather quickly. Blisters and ulcers may be seen on the sclerotic surfaces (Fig. 1c). Sometimes subcutaneous fat and fascia are also involved, resulting in eosinophilic fasciitis-like appearance (1, 4, 21). Acrosclerosis and Raynaud phenomenon, which are commonly seen in progressive scleroderma, are not frequent in sclerodermoid chronic GVHD. In our patients with chronic cutaneous GVHD, 12 had sclerodermoid lesions, 14 had post-inflammatory hypopigmentation and hyperpigmentation, and 4 had poikilodermatous alterations (Fig. 1d). Hyperpigmentation is a well-documented feature of cutaneous GVHD, and is usually accepted to be post-inflammatory (4, 21, 30). It is emphasized that *de novo* melanoderma can also be a sign of cutaneous GVHD (30). Two of our patients developed vitiligo.

All our patients experienced dryness of the skin; 12 had intense dryness and 1 patient developed acquired ichthyosis (31). Diffuse alopecia occurred in 45.7% of patients and it was severe in cases with generalized sclerodermoid chronic GVHD.

In chronic GVHD oral lesions are seen in approximately 80% of the patients. Oral manifestations may include xerostomia, lichen planus-like changes, reticular whitish plaques, atrophy of the oral mucosa, erosions and ulcerations, and submucosal fibrosis (4, 21, 22, 32). Oral mucosa involvement may be the sole finding in chronic GVHD. Sicca syndrome of the eyes and the mouth can be seen and pyogenic granuloma formation has been reported as a rare finding (1, 4, 21, 33). Oral mucosa involvement was present in 60.9% of our chronic GVHD patients and six patients had only mucosal lesions without any skin involvement.

Nail changes are usually similar to the nail lesions in lichen planus (4, 21, 34) and may be the first signs of chronic GVHD (35). Nail involvement rate was 31.3% in our patients and the most commonly encountered alterations were longitudinal streaks and roughness of the nail plates.

Acute GVHD is an important factor in reducing survival after haematopoietic cell transplantation. The most important cause of mortality is infections that occur most frequently during the third and fourth months (1, 4, 21, 22). In our study, three of the patients died with severe acute GVHD. Chronic GVHD has direct influence on both mortality and morbidity. In some series 40% mortality rates have been reported for chronic GVHD. The most important causes of mortality are infections, liver dysfunction and cachexia (21). Of the 67 patients that we studied, 7 cases died due to complications of chronic GVHD.

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